

(FILE 'HOME' ENTERED AT 17:17:05 ON 01 SEP 2004)

FILE 'MEDLINE, CANCERLIT' ENTERED AT 17:17:55 ON 01 SEP 2004

L1	0 S E2F1 PROMOTER AND ADENOVIRAL AND PRB
L2	0 S E2F1 PROMOTER AND ADENOVIRAL
L3	0 S E2F PROMOTER AND ADENOVIRAL AND PRB
L4	21 S CR2 AND E1A AND E2F
L5	11 DUP REM L4 (10 DUPLICATES REMOVED)
L6	1692226 S TUMOR OR CANCER
L7	4072 S E2F1 OR E2F
L8	1328 S L7 AND PROMOTER
L9	628 S L8 AND L6
L10	112 S L9 AND ADENOVIR?
L11	60 S L10 AND E1A
L12	33 DUP REM L11 (27 DUPLICATES REMOVED)

L12 ANSWER 2 OF 33 MEDLINE on STN
 AN 2003154263 MEDLINE
 DN PubMed ID: 12670895
 TI An oncolytic **adenovirus** selective for retinoblastoma
tumor suppressor protein pathway-defective tumors: dependence on
E1A, the **E2F-1 promoter**, and viral replication
 for selectivity and efficacy.
 AU Jakubczak John L; Ryan Patricia; Gorziglia Mario; Clarke Lori; Hawkins
 Lynda K; Hay Carl; Huang Ying; Kaloss Michele; Marinov Anthony; Phipps
 Sandrina; Pinkstaff Anne; Shirley Pamela; Skripchenko Yelena; Stewart
 David; Forry-Schaudies Suzanne; Hallenbeck Paul L
 CS Genetic Therapy, Inc, Gaithersburg, Maryland 20878, USA.
 SO Cancer research, (2003 Apr 1) 63 (7) 1490-9.
 Journal code: 2984705R. ISSN: 0008-5472.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200304
 ED Entered STN: 20030403
 Last Updated on STN: 20030423
 Entered Medline: 20030422
 AB The use of oncolytic **adenoviruses** as a **cancer**
 therapeutic is dependent on the lytic properties of the viral life cycle,
 and the molecular differences between **tumor** cells and nontumor
 cells. One strategy for achieving safe and efficacious **adenoviral**
 therapies is to control expression of viral early gene(s) required for
 replication with **tumor-selective promoter(s)**,
 particularly those active in a broad range of **cancer** cells. The
 retinoblastoma **tumor** suppressor protein (Rb) pathway is
 dysregulated in a majority of human cancers. The human **E2F-1**
promoter has been shown to be selectively activated/derepressed in
tumor cells with a defect in the Rb pathway. Ar6pAE2fE3F and
 Ar6pAE2ffF are oncolytic **adenoviral** vectors (with and without the
 viral E3 region, respectively) that use the **tumor-selective**
E2F-1 promoter to limit expression of the viral
E1A transcription unit, and, thus, replication, to **tumor**
 cells. We demonstrate that the antitumor activity of Ar6pAE2ffF in vitro
 and in vivo is dependent on the **E2F-1 promoter** driving
E1A expression in Rb pathway-defective cells, and furthermore,
 that its oncolytic activity is enhanced by viral replication. Selective
 oncolysis by Ar6pAE2ffF was dependent on the presence of functional
E2F binding sites in the **E2F-1 promoter**, thus
 linking antitumor viral activity to the Rb pathway. Potent antitumor
 efficacy was demonstrated with Ar6pAE2ffF and Ar6pAE2fE3F in a xenograft
 model following intratumoral administration. Ar6pAE2ffF and Ar6pAE2fE3F
 were compared with Addl1520, which is reported to be molecularly identical
 to an E1B-55K deleted vector currently in clinical trials. These vectors
 were compared in in vitro cytotoxicity and virus production assays, after
 systemic delivery in an in vivo **E1A**-related hepatotoxicity
 model, and in a mouse xenograft **tumor** model after intratumoral
 administration. Our results support the use of oncolytic
adenoviruses using **tumor-selective promoter(s)**
 that are activated or derepressed in **tumor** cells by virtue of a
 particular defective pathway, such as the Rb pathway.

L12 ANSWER 19 OF 33 CANCERLIT on STN

AN 1998641306 CANCERLIT

DN 98641306

TI Mechanism of action of the Rb **tumor** suppressor (Meeting abstract).

AU Anonymous

CS Washington University School of Medicine, St. Louis, MO 63110.

SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 648.

ISSN: 0197-016X.

DT (MEETING ABSTRACTS)

LA English

FS Institute for Cell and Developmental Biology

EM 199807

ED Entered STN: 19980713

Last Updated on STN: 19980713

AB The retinoblastoma protein (Rb) is a **tumor** suppressor that regulates progression from G1 to S phase of the cell cycle. Rb is a transcriptional repressor selectively targeted to promoters through interaction with the **E2F** family of cell cycle transcription factors. When Rb is tethered to **promoter** through **E2F**, it blocks **E2F** activity and binds surrounding transcription factors, preventing their interaction with basal transcription complex, and thus inhibiting cell cycle gene transcription. The Rb-**E2F** interaction was examined by transfecting a mutant form of **E2F**-1 lacking transactivation domain and Rb binding site but retaining the DNA binding domain. This dominant-negative form of **E2F**-1 transformed rat embryo fibroblasts, suggesting: (1) the transactivating domain of **E2F**-1 is not required for cells to progress from G1 to S phase; (2) repressor activity of Rb, bound to **E2F**, regulates G1/S transition. Additionally, we found that this dominant-negative form of **E2F**-1 prevented growth suppression by p16 **tumor** suppressor protein. p16 is a cyclin dependent kinase (cdk) inhibitor that blocks the activity of D cyclins in complex with cdk 4 or 6. Cdk4/6 in complex with D cyclins can phosphorylate and inactivate Rb, allowing progress from G1 to S. Our results suggest that Rb-**E2F** may be the ultimate target of p16 in cells. Two domains in the Rb pocket, A and B, conserved across species and in the Rb-related proteins p107 and p130, are both required for repressor activity. The non-conserved spacer separating A and B is not required. Neither A nor B alone had repressor activity, but repressor activity was observed when the domains were coexpressed on separate proteins. Transfection assays suggest one domain can recruit the other to the **promoter** to form a repressor motif that can both interact with **E2F** and have a dominant inhibitory effect on transcription. A and B interact directly, and mutations disrupting this interaction inhibit repressor activity. The Rb pocket was originally defined as the binding site for oncoproteins from DNA **tumor** viruses such as **adenovirus E1a**. We have found that **E1a** interacts with a site formed by the interaction of A and B, and that this interaction with A and B induces or stabilizes A-B interaction. The A-B repressor motif is shared by Rb-related protein p107. Phosphorylation of Rb by G1 cdks inactivates the protein, allowing cells to progress from G1 to S phase. The A-B interaction forming the repressor motif is blocked by G1 cdk phosphorylation, blocking repressor activity. This A-B repressor motif is the first example of a cdk-regulated transcriptional repressor.

L12 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 3
 AN 2002344096 MEDLINE
 DN PubMed ID: 12086848
 TI Selectively replicating **adenoviruses** targeting deregulated
E2F activity are potent, systemic antitumor agents.
 AU Johnson Leisa; Shen Annie; Boyle Larry; Kunich John; Pandey Kusum; Lemmon
 Marilyn; Hermiston Terry; Giedlin Marty; McCormick Frank; Fattaey Ali
 CS Onyx Pharmaceuticals, Richmond, California 94806, USA..
 ljohnson@exelixis.com
 SO Cancer cell, (2002 May) 1 (4) 325-37.
 Journal code: 101130617. ISSN: 1535-6108.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200207
 ED Entered STN: 20020628
 Last Updated on STN: 20020726
 Entered Medline: 20020725
 AB We have engineered a human **adenovirus**, ONYX-411, that
 selectively replicates in human **tumor** cells, but not normal
 cells, depending upon the status of their retinoblastoma **tumor**
 suppressor protein (pRB) pathway. Early and late viral gene expression as
 well as DNA replication were significantly reduced in a functional
 pRB-pathway-dependent manner, resulting in a restricted replication
 profile similar to that of nonreplicating **adenoviruses** in normal
 cells both in vitro and in vivo. In contrast, the viral life cycle and
tumor cell killing activity of ONYX-411 was comparable to that of
 wild-type **adenovirus** following infection of human **tumor**
 cells in vitro as well as after systemic administration in **tumor**
 -bearing animals.